CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20983

STATISTICAL REVIEW(S)

JAN 14 1999

Statistical Review and Evaluation
Clinical

NDA#: 20-983

APPLICANT: Glaxo Wellcome Inc.

NAME OF DRUG: Ventolin HFA

INDICATION: Treatment of Asthma and Exercise Induced Bronchospasm in adults and children 4 years of age and greater

DOCUMENTS REVIEW: Volumes 1.1, 1.49, 1.56,1.73,1.87 and SAS datasets dated June 30, 1998 ; Volume 13.1 dated October 26, 1998; and an unnumbered volume and SAS datasets dated November 11, 1998.

This review pertains to two studies in adults with asthma (SALA3002 and SALA3005), one study in children with asthma (SALA3006) , and one study in exercise induced asthma (SALB2001).

The medical officer for this submission is A. Trontell, M.D. (HFD-570), with whom this review was discussed.

I. Background

The sponsor supplied the results of Study SALA3002 excluding Dr. Edward's patients in the October 26, 1998 submission. In a telephone conversation with the sponsor on November 4, 1998, SAS datasets of the derived variables (Onset, Duration, Peak, and AUC(bl)) were requested for the three asthma studies. The data from Dr. Edward's patients were deleted in Study SALA3002. 95% confidence limits were requested for the difference between treatments for the derived variables. This reviewer also requested an explanation of why the variable percent fall in FEV_1 in the SAS dataset for Study SALB2001 did not agree with the listings in the study report. The sponsor provided this information in the November 11, 1998 submission. The percent falls in FEV_1 in the SAS dataset were based on the investigators' calculations and were not always correct. The data listings were correct and percent falls in FEV_1 were calculated correctly at the time of analysis. In the asthma studies, 95% confidence limits were only calculated for peak and AUC (bl) because the other derived variables were tested using non-parametric tests.

Peak effect and AUC (bl) were analyzed using an analysis of variance F-test controlling for investigator. Onset, duration and time to peak were analyzed using the non-parametric van Elteren test controlling for investigator.

[The primary analysis in the protocol is a repeated measures analysis of the serial FEV_1 values. This analysis is not discussed in this review because the reviewer is focusing on the derived measures of the serial FEV_1 measurements. The conclusions from these analyses were similar, however, to those based on the derived variables. The reviewer thinks that the repeated measures analysis overweights the first hour of assessments because of the need to capture onset of effect.]

B. Results

A total of 313 patients were randomized to treatment (104 to placebo HFA, 101 to albuterol HFA, and 108 to albuterol CFC). Three of these patients were randomized at the time of run-in Visit A and, as such, their Visit A data was used as their Day 1 visit. These three patients therefore did not have a Visit A evaluation. Thirty-seven patients did not complete the study. There were 276 patients (86 placebo, 91 albuterol HFA, and 99 albuterol CFC) who completed the study. More than half (57%) of the withdrawals were for "other" reasons (primarily protocol violations and non-compliance). There were 25 investigator sites. The data from five sites (Kaiser, A. Weinstein, Livezey, Selner/Volz, and Karpel) were combined for all analyses because of small sample size.

The treatment groups were comparable in demographic variables and baseline efficacy variables.

The data from Dr. Edward's site were not included in the analyses of derived variables (although included in the patient numbers above) because of restrictions placed upon Dr. Edwards by the FDA's Division of Scientific Investigations. Otherwise the analyses were intent-to-treat analyses with the restriction that no data was imputed for a patient at Week 6 or Week 12 if the patient did not have serial PFTs at those clinic visits.

Table 1 contains the means and p-values comparing treatments for the derived variables at Day 1, Week 6 and Week 12. Both albuterol treatments were significantly different ($p<0.001$) from placebo at all evaluations for all of the derived variables. No significant difference between albuterol HFA and albuterol CFC were seen in this study.

C. Reviewer's Comments

There was no suggestion of treatment-by-center interaction in the analyses of peak effect and AUC(bl). The analysis of the derived measures of FEV_1 showed efficacy for albuterol HFA. There is a suggestion in the data that the CFC formulation might be numerically more effective than the HFA formulation (see Table 1).

III. Study SALA3005

A. Study Design and Method of Analysis

This study was similar to Study SALA3002 with the exception that there was no albuterol CFC run-in and no Visit A.

B. Results

A total of 297 patients were randomized to treatment (97 to placebo HFA,101 to albuterol HFA, and 99 to albuterol CFC). Of these 297 patients, 249 patients (79 placebo, 84 albuterol HFA, and 86 albuterol CFC) completed the trial. There were 48 withdrawals (18 placebo, 17 albuterol HFA, and 13 albuterol CFC). Of these withdrawals, 22 (7 placebo, 8 albuterol HFA, and 7 albuterol CFC) were for lack of efficacy and 21 (10 placebo, 7 albuterol HFA, and 4 albuterol CFC) were for "other" reasons. There were 20 centers in this study. The data from three small centers (Tarpay, Pollard, and Flescher) were combined for all analyses.

The treatment groups were comparable at baseline in demographic and baseline pulmonary function.

Table 2 contains the means and p-values comparing treatments for the derived variables at Day 1, Week 6 and Week 12. Both albuterol treatments were significantly different ($p<0.001$) from placebo at all evaluations for all of the derived variables. The only significant differences between albuterol HFA and albuterol CFC were seen in onset and peak effect at Day 1 in this study.

C. Reviewer's Comments

There was no suggestion of treatment-by-center interaction in the analyses of peak effect and AUC(bl). The analysis of the derived measures of FEV_1 showed efficacy for albuterol HFA. There is a suggestion in the data that the CFC formulation might be numerically more effective than the HFA formulation (see Table 2).

IV. Study SALA3006

A. Study Design and Method of Analysis

This study is similar to study SALA3005 except that it was conducted in children 4-11 years of age and had only a two-week treatment period. All children had serial pulmonary function assessed by PEFR using a Mini-Wright Peak Flow Meter. Some children 4-5 years of age were not able to perform spirometry and hence FEV_1 could not be assessed on all children. Therefore, this reviewer will assess efficacy and comparability using PEFR.

B. Results

There were 135 (43 placebo and 46 for both albuterol treatments) children enrolled into the study. Of these 135 children, 118 (36 placebo and 41 for both albuterol treatments) completed the study. Eleven of the 17 withdrawals were for "other" reasons, primarily protocol violations and non-compliance. There were 11 centers in this study.

The treatment groups were comparable in demographic variables and baseline efficacy variables.

Table 3 contains the means and p-values comparing treatments for the derived variables at Day 1 and Week 2. Both albuterol treatments were significantly different from placebo at both evaluations for most of the derived variables. No significant difference between albuterol HFA and albuterol CFC were seen in this study.

C. Reviewer's Comments

There was a suggestion of treatment-by-center interaction in the analyses of AUC(bl) at Day 1 (p=0.0411). If the placebo treatment is deleted, the p-value of the treatment by center interaction is 0.385. Therefore, the treatment-by-center interaction hasn't affected the comparisons of the albuterol groups. The analysis of the derived measures of FEV_1 showed efficacy for albuterol HFA. There is little evidence that the CFC formulation might be numerically more effective than the HFA formulation in this study.

V. Study SALB2001

A. Study Design and Method of Analysis

This was a single dose, single center, double blind, placebo controlled three-way crossover study comparing placebo, albuterol HFA and albuterol CFC in adult or adolescent patients 12-45 years of age. There was a washout period of at least 1day between treatments. Subjects had to have a fall on exercise challenge of at least 20% in percent predicted FEV_1 during the 60 minutes after exercising to enter the trial. Pulmonary function tests were conducted at 5 minutes pre-exercise challenge and at 5, 10, 15, 20, 25, 30 and 60 minutes after exercise challenge.

The primary efficacy measure was maximum percent fall in FEV_1 during the 60 minutes after exercise challenge. The primary analysis was an analysis of variance (ANOVA) appropriate for a crossover model. The model included terms for subject, period and treatment. Treatment-by-period interaction and carry-over were evaluated in supplementary analyses.

B. Results

Twenty-four subjects were randomized into the study. One subject withdrew before receiving albuterol HFA because the 15-minute pre-dosing FEV_1 varied by >15% from

the screening pre-exercise FEV_1. This subject received the other two treatments and was included in the analysis.

The table below provides the adjusted means of the treatment groups and the 95% confidence limits of the two albuterol groups for percent fall in FEV_1.

	Placebo	Albuterol HFA	Albuterol CFC
Adjusted mean (%)	33.7	15.4	14.9
P-value compared to placebo		<0.001	<0.001
Albuterol CFC-Albuterol HFA			
Difference (%)			-0.5
P-value			0.848
95% confidence limits (%)			(-5.3,4.4)

The mean percent falls in FEV_1 of the patients when on both albuterol treatments were significantly different from placebo with rough comparability between the albuterol treatments.

There was no evidence of carryover (p=0.267), or a treatment by period interaction (p=0.340).

VI. Label

The sponsor combined the results of the results of Study SALA3002 and SALA3005 in the label. This is not the usual practice. If such combination is allowed, the sponsor provided the results of the combined data excluding the data for Dr. Edwards in their November 11, 1998 submission. Those results should be considered at the time of negotiating the label.

VII. Overall Conclusions

Studies SALA3002, SALA3005 and SALA3006 showed both albuterol formulations to be significantly better than placebo with rough comparability between albuterol formulations for the derived variables from the PFTs [onset, duration, peak, time to peak and AUC(bl) of FEV_1]. There was a slight suggestion is Studies SALA3002 and SALA3005, but not in Study SALA3006, that the CFC formulation might be numerically more effective. The sample sizes of the studies were adequate to detect major differences between the albuterol groups.

Study SALB2001 showed both albuterol formulations were equally effective compared to placebo for percent fall in FEV_1.

/S/

James R. Gebert, Ph.D.
Mathematical Statistician HFD-715

Concur: Dr. Wilson 1/12/99

Dr. Nevius 1/14/99

This review contains 7 pages of text and 3 pages of tables.
cc:
Archival NDA 20-983
HFD-570
HFD-570/Dr. Trontell
HFD-570/Ms. Jani
HFD-715/Div. File,Chron
HFD-715/Dr. Gebert
HFD-715/Dr. Wilson

TABLE 1

Means or medians* of derived variables from Serial FEV_1 (l/min) and p-values comparing treatment At Day 1 in Study SALA3002

Variable	Treatment group			P-value		
Measurement	Placebo	Albuterol HFA	Albuterol CFC	Placebo Vs Alb. HFA	Placebo Vs Alb. CFC	Alb HFA Vs Alb CFC
Onset (hours)*	6.00	0.07	0.06	<0.001	<0.001	0.205
Duration (hours)*	0.00	3.09	3.67	<0.001	<0.001	0.198
Peak (% change)	14.0	28.1	30.2	<0.001	<0.001	0.209
Time to Peak (hours)*	3.0	1.0	1.0	<0.001	<0.001	0.653
AUC (bl) (%)	0.81	2.49	2.72	<0.001	<0.001	0.249

Means or medians* of derived variables from Serial FEV_1 (l/min) and p-values comparing treatment At Week 6 in Study SALA3002

Variable	Treatment group			P-value		
Measurement	Placebo	Albuterol HFA	Albuterol CFC	Placebo Vs Alb. HFA	Placebo Vs Alb. CFC	Alb HFA Vs Alb. CFC
Onset (hours)*	6.00	0.38	0.07	<0.001	<0.001	0.113
Duration (hours)*	0.00	0.40	1.97	<0.001	<0.001	0.325
Peak (% change)	13.0	23.6	27.5	<0.001	<0.001	0.081
Time to Peak (hours)*	4.0	1.0	0.5	<0.001	<0.001	0.789
AUC (bl) (%)	0.83	1.86	2.00	<0.001	<0.001	0.522

Means or medians* of derived variables from Serial FEV_1 (l/min) and p-values comparing treatment At Week 12 in Study SALA3002

Variable	Treatment group			P-value		
Measurement	Placebo	Albuterol HFA	Albuterol CFC	Placebo Vs Alb. HFA	Placebo Vs Alb. CFC	Alb. HFA Vs Alb CFC
Onset (hours)*	6.00	0.18	0.11	<0.001	<0.001	0.849
Duration (hours)*	0.00	1.03	1.65	<0.001	<0.001	0.484
Peak (% change)*	13.4	23.2	23.5	<0.001	<0.001	0.777
Time to Peak (hours)*	3.0	1.0	1.0	<0.001	<0.001	0.656
AUC (bl) (%)	0.82	1.72	1.78	0.001	<0.001	0.634

TABLE 2

Means or medians* of derived variables from Serial FEV_1 (l/min) and p-values comparing treatment At Day 1 in Study SALA3005

Variable	Treatment group			P-value		
Measurement	Placebo	Albuterol HFA	Albuterol CFC	Placebo Vs Alb. HFA	Placebo Vs Alb. CFC	Alb HFA Vs Alb CFC
Onset (hours)*	6.00	0.07	0.05	<0.001	<0.001	0.011
Duration (hours)*	0.00	3.54	3.73	<0.001	<0.001	0.086
Peak (% change)	14.7	29.6	35.6	<0.001	<0.001	0.011
Time to Peak (hours)*	3.0	1.0	1.0	<0.001	<0.001	0.804
AUC (bl) (%)	0.81	2.49	2.79	<0.001	<0.001	0.314

Means or medians* of derived variables from Serial FEV_1 (l/min) and p-values comparing treatment At Week 6 in Study SALA3005

Variable	Treatment group			P-value		
Measurement	Placebo	Albuterol HFA	Albuterol CFC	Placebo Vs Alb. HFA	Placebo Vs Alb. CFC	Alb HFA Vs Alb. CFC
Onset (hours)*	6.00	0.07	0.07	<0.001	<0.001	0.103
Duration (hours)*	0.00	2.07	2.41	<0.001	<0.001	0.763
Peak (% change)	11.3	25.8	28.9	<0.001	<0.001	0.140
Time to Peak (hours)*	3.0	1.0	1.0	<0.001	<0.001	0.843
AUC (bl) (%)	0.44	1.69	1.89	<0.001	<0.001	0.261

Means or medians* of derived variables from Serial FEV_1 (l/min) and p-values comparing treatment At Week 12 in Study SALA3005

Variable	Treatment group			P-value		
Measurement	Placebo	Albuterol HFA	Albuterol CFC	Placebo Vs Alb. HFA	Placebo Vs Alb. CFC	Alb. HFA Vs Alb CFC
Onset (hours)*	6.00	0.07	0.07	<0.001	<0.001	0.403
Duration (hours)*	0.00	2.92	2.48	<0.001	<0.001	0.351
Peak (% change)	10.2	26.9	29.0	<0.001	<0.001	0.362
Time to Peak (hours)*	3.0	0.5	1.0	<0.001	<0.001	0.103
AUC (bl) (%)	0.25	1.84	1.98	<0.001	<0.001	0.465

TABLE 3

Means or medians* of derived variables from Serial PEFR (l/min) and p-values comparing treatment At Day 1 in Study SALA3006

Variable	Treatment group			P-value		
Measurement	Placebo	Albuterol HFA	Albuterol CFC	Placebo Vs Alb. HFA	Placebo Vs Alb. CFC	Alb HFA Vs Alb CFC
Onset (hours)*	6.0	0.08	0.20	<0.001	0.024	0.159
Duration (hours)*	0.00	2.58	1.09	0.002	0.052	0.221
Peak (% change)	21.9	35.8	31.5	<0.001	0.018	0.276
Time to Peak (hours)*	3	1	2	0.062	0.151	0.689
AUC (bl) (%)	93	189	192	0.002	0.003	0.886

Means or medians* of derived variables from Serial PEFR (l/min) and p-values comparing treatment At Week 2 in Study SALA3006

Variable	Treatment group			P-value		
Measurement	Placebo	Albuterol HFA	Albuterol CFC	Placebo Vs Alb. HFA	Placebo Vs Alb. CFC	Alb HFA Vs Alb. CFC
Onset (hours)*	6.0	0.16	0.19	0.003	0.001	0.892
Duration (hours)*	0.00	1.61	1.86	0.010	0.003	0.648
Peak (% change)	19.7	28.0	26.6	0.018	0.025	0.892
Time to Peak (hours)*	3	1	2	<0.001	0.001	0.552
AUC (bl) (%)	79	153	166	0.009	0.002	0.566

STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

NDA Number:	**20-983**
Applicant:	**Glaxo Wellcome, Inc.**
Name of Drug:	**Ventolin® HFA (Albuterol Sulfate, USP Inhalation Aerosol)**
Statistical Reviewer:	**Feng Zhou, HFD-715**
Chemistry Reviewer:	**Craig Bertha, Ph.D., HFD-570**
Document Reviewed:	**Attachment 32.1 - Stability Commitments (Manufacturing, and Controls, Volume 1 and 2, dated June 29, 2000)**

I. Introduction

The sponsor submitted the stability data to support its proposed 18-month shelf life for Ventolin® HFA. Data of three batches (6ZX012, 6ZX013, and 6ZX015) stored with protective packaging (termed "protected") in an "inverted" position at 25°C/60%RH were included.

II. Stability Parameters

The following is a list of stability parameters and their specifications the sponsor used to establish the stability for Ventolin® HFA.

III. Sponsor's Stability Analysis

The data submitted by the sponsor were summarized in Table A below.

Table A

Summary of all stability data submitted by the sponsor

			Time Points (Month)							
Test	Storage	Batch	0	3	6	9	12	18	24	36
Mean albuterol content per actuation Beginning-of-use	25°C/60%RH									
Mean albuterol content per actuation End-of-use	25°C/60%RH									
Throat by cascade impaction	25°C/60%RH									
Sum of stages 0, 1, and 2, by cascade impaction	25°C/60%RH									
Sum of stages 3, 4, and 5, by	25°C/60%RH									
Sum of stages 6, 7, and filter, by	25°C/60%RH									
Mean weight of canister contents	25°C/60%RH									
Mean albuterol content per canister	25°C/60%RH									

S = Submitted in paper copy
E = Submitted in electronic copy (Stats Tables.xls)

File name: STAB20_983.doc

The sponsor performed statistical analyses based on data of three batches up to 36 months stored with protective packaging (termed "Protected") in an "Inverted" position at 25°C/60%RH. The expiration dates were estimated based on following 6 parameters:

There was no statistical evaluation done by the sponsor on the data of content of albuterol-related impurities or the albuterol content per canister. The sponsor claimed that the stability data for these tests clearly demonstrated no change after long-term or high-stress storage and hence a statistical evaluation would provide no additional information. Table B summarizes the results based on the six parameters, respectively.

Table B

Sponsor's estimated expiration dating periods for Primary Albuterol/GR106642X Inhalation Aerosol based on stability data of batches stored at 25°C/60%RH inverted, protected

Analysis Parameter	*Model*[1]	*Least Favorable Study*[2]	*Predicted Expiry*
Mean albuterol content per actuation, beginning-of-use	Common Slopes		33 months
Mean albuterol content per actuation, end-of-use	Common Slopes		0 months
Mean albuterol content per actuation, end-of-use[3]	Combined		> 36 months
Throat, by	Common Slopes		> 36 months
Sum of stages 0, 1, and 2, by	Combined		> 36 months
Sum of stages 3, 5, and 4, by	Common Slopes		> 36 months
Sum of stages 6 and 7, and filter, by	Combined		> 36 months

[1] Models: Combined = Common slope and common intercept.
Common Slopes = Common slope but separate intercepts.
Not combined = Separate slopes and separate intercepts.
[2] Least Favorable Study = Batch with shortest estimated expiration dating period.
[3] This analysis was performed excluding data at 3 months and 18 months.

File name: STAB20_983.doc

The statistical methods used by the sponsor were, generally, in accordance with FDA's "Guidelines for Submitting Documentation for the Stability of Human Drugs Biologics." (February 1987)

III. Reviewer's Stability Analysis

This reviewer analyzed the data in accordance with FDA's "Guidelines for Submitting Documentation for the Stability of Human Drugs Biologics." Data up to thirty-six months from three batches (6ZX012, 6ZX013, and 6ZX015) stored with protective packaging (termed "protected") in an "inverted" position at 25°C/60%RH were analyzed. Data submitted in both paper copy and electronic copy were used in the reviewer's analyses.

Table C summarizes the results based on the eight parameters, respectively.

The shortest estimated expiration date is 6 months for Batch 6ZX013 based on the parameter mean albuterol content per actuation at the end-of-use. Figure A shows that the observations at 3 and 18 months for the parameter were outside of the upper specification limit for Batch 6ZX013.

In general, it is not statistically acceptable to perform a statistical analysis by excluding the extreme data points without valid justifications. This reviewer consulted with the chemistry reviewer (Dr. Bertha) and at his direction performed the statistical analysis using the data from batch of 7ZX027 (split into three sub-batches a, b, and c by virtue of the use of three distinct incoming to-be-marketed type canister lots). The data are showed in Table D. The estimated expiration-dating period based on these three sub-batches for the parameter mean albuterol content per actuation at the end-of-use is 63 months. The fitted regression line, the lower and upper specification limits of the fitted line are showed in Figure B.

V. Conclusion

The results of the sponsor's analysis did support its 18-month estimated expiration-dating period for the product with some data deleted.

The results of this reviewer's analysis using data of the three batches (6ZX012, 6ZX013, and 6ZX015) show a 6-month estimated expiration date for all the package types of Ventolin® HFA (Albuterol Sulfate, USP Inhalation Aerosol). The above 6-month estimated expiration-dating period for the drug product is determined by the shortest estimated period based on the parameter mean albuterol per actuation at the end-of-use for Batch 6ZX013. But, the results of analysis using the data of three sub-batches (7ZX027a, 7ZX027b, and 7ZX027c) show that the expiration-dating period based on the same parameter can be increased to 63 months.

Therefore, the sponsor's proposed 18-month expiration date is supported by the stability data for the two primary stability batches 6ZX012 and 6ZX015. Because of the out-of-specification results for the mean albuterol per actuation at the end-of-use for the 3 and 18 month time-point for the 6ZX013 primary stability batch, this batch did not support the proposed 18-month expiration dating period. However, the sponsor had also submitted an additional commercial scale stability batch to the application 7ZX027 (split into three sub-batches a, b, and c by virtue of the use of three distinct incoming to-be-marketed type canister lots). An analogous analysis of the predicted expiry of this batch based on the parameter of mean albuterol content per actuation at the end-of-use did support the proposed 18-month expiration-dating period for the product.

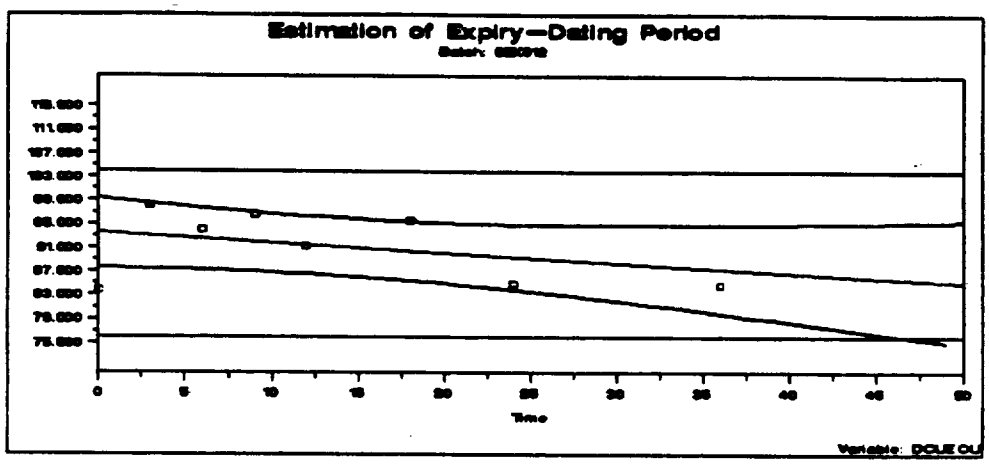
File name: STAB20_983.doc

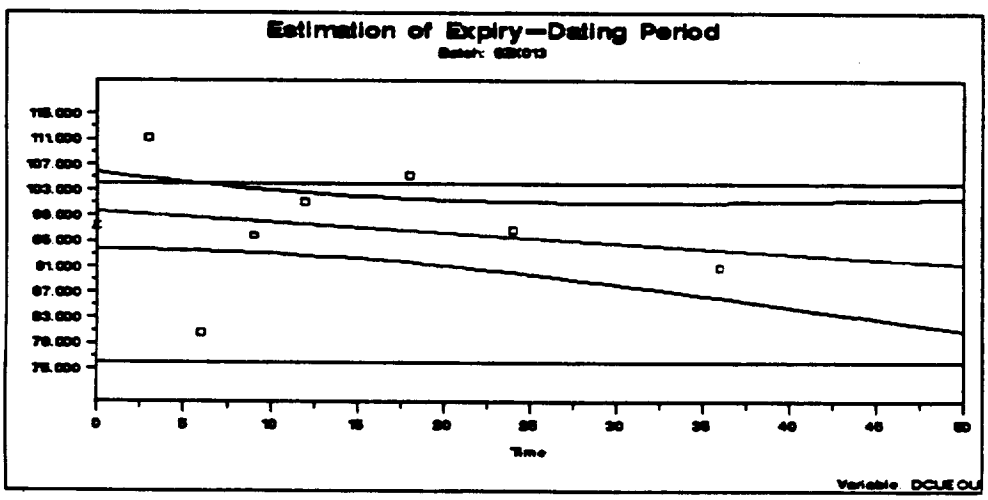
Table C

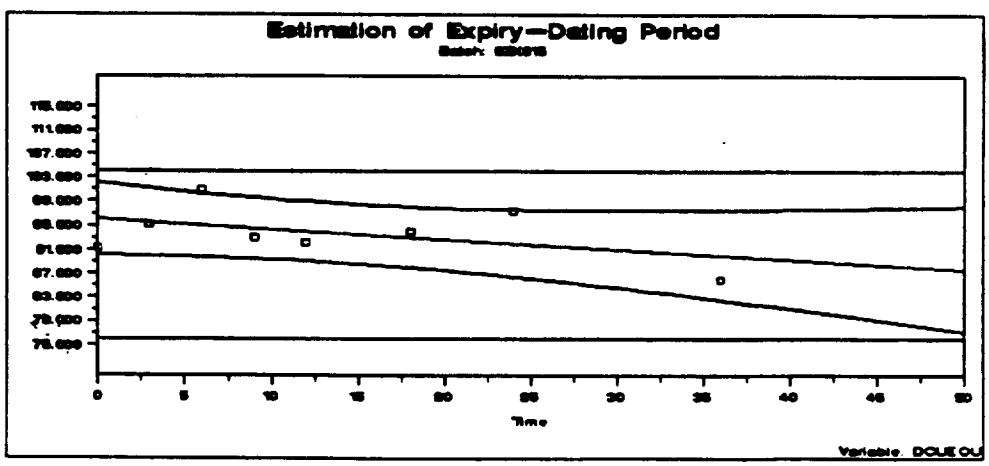
Expiry date analysis for Ventolin® HFA (Albuterol Sulfate, USP Inhalation Aerosol)

Test	Specification	Model Selection	Batch	Fitted Line	Expiry Date
Mean albuterol content per actuation beginning-of-use		The regression lines are parallel			46 33 48
Mean albuterol content per actuation end-of-use		The regression lines are parallel			46 6 53
Throat by		The regression lines are parallel			65 82 86
Sum of stages 0, 1, and 2, by		All batches are pooled			48
Sum of stages 3, 4, and 5, by		The regression lines are parallel			71 86 89
Sum of stages 6, 7, and filter, by		All batches are pooled			45
Mean weight of canister contents		The regression lines have separate slopes & intercepts			39 37 39
Mean albuterol content per canister		The regression lines are parallel			83 35 74

Figure A
Expiry date analysis for Ventolin® HFA,
For Mean albuterol content per actuation at the end-of use
For Batches 6ZX012, 6ZX013, and 6ZX015







File name: STAB20_983.doc

Table D

The stability data from three sub-batches for parameter

Mean albuterol content per actuation, end-of-use

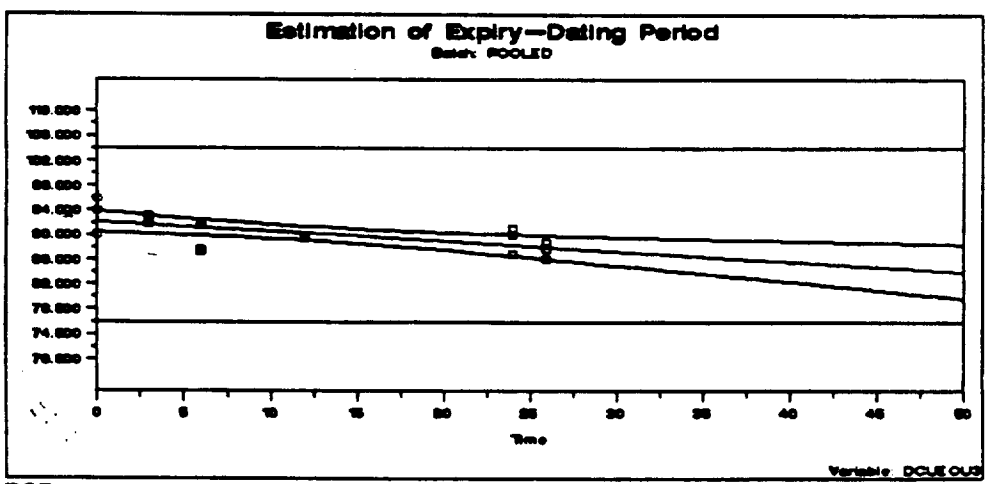
DCUEOU	0.05	2	76	104	7ZX027a	0	90.08
DCUEOU	0.05	2	76	104	7ZX027a	3	91.94
DCUEOU	0.05	2	76	104	7ZX027a	6	91.56
DCUEOU	0.05	2	76	104	7ZX027a	12	89.92
DCUEOU	0.05	2	76	104	7ZX027a	24	86.94
DCUEOU	0.05	2	76	104	7ZX027a	26	86.21
DCUEOU	0.05	2	76	104	7ZX027b	0	94.06
DCUEOU	0.05	2	76	104	7ZX027b	3	92.59
DCUEOU	0.05	2	76	104	7ZX027b	6	87.21
DCUEOU	0.05	2	76	104	7ZX027b	12	89.493
DCUEOU	0.05	2	76	104	7ZX027b	24	90.03
DCUEOU	0.05	2	76	104	7ZX027b	26	88.95
DCUEOU	0.05	2	76	104	7ZX027c	0	95.91
DCUEOU	0.05	2	76	104	7ZX027c	3	93.26
DCUEOU	0.05	2	76	104	7ZX027c	6	87.66
DCUEOU	0.05	2	76	104	7ZX027c	12	
DCUEOU	0.05	2	76	104	7ZX027c	24	91.14
DCUEOU	0.05	2	76	104	7ZX027c	26	87.66

Test	*Specification*	*Model Selection*	*Batch*	*Fitted Line*	*Expiry Date*
Mean albuterol content per actuation end-of-use	76 - 104 µg (85-115% of LC)	All batches are pooled	7ZX027a 7ZX027b 7ZX027c	Y=92.1847 - 0.1618 * Time	63

Figure B

The stability data from three sub-batches for parameter

Mean albuterol content per actuation at the end-of-use



-EOF

File name: STAB20_983.doc

/s/

Feng Zhou
12/15/00 02:34:35 PM
BIOMETRICS

Karl Lin
12/18/00 09:27:16 AM
BIOMETRICS
Concurred